## RESPONSE

### I. Status of the Claims

Claims 1 and 5-7 are presently pending in the case.

### III. Rejection of Claims Under 35 U.S.C. § 101

The Action continues to reject the claims under 35 U.S.C. § 101, allegedly because the claimed invention lacks support by either a specific and substantial asserted utility or a well established utility. Applicants respectfully traverse based on the arguments presented in the Applicants' previous responses and those detailed below.

The Action disagrees with Applicants' logical assertion, based on the evidence that the sequences of the present invention encode an isoform of an ATP-binding cassette transporter protein as identified by those of skill in the art, in no way associated with Applicants. This clearly indicates that Applicants assertions are credible. Given the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, this is clear evidence that those skilled in the art would have recognized the function and activity of the protein encoded by the sequences of the present invention, there can, therefore, be no question that Applicants' asserted utility for the described sequences is "credible." According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

The Action fails to accept, as credible, Applicant's assertion that the present invention is a human transporter protein, in particular, a splice variant that encodes and isoform of the ATP-binding cassette, sub-family C, member 11; multi-resistance protein 8. ATP-binding cassette transporters are known to the art to be frequently associated with multiple drug resistance by cancer cells. Mutations in these genes can cause accelerated removal of chemotherapeutic agents Similar MDR encoding sequences, uses, and applications that are germane to the proteins encoded by the sequences of the present invention, were described in issued U.S. Patents Nos. 5,198,344 and 5,866,699 which were incorporated by reference in their entirety into the present application.

This assertion is clearly credible and was supported by the evidence provided in Exhibits E and F, submitted with Applicants' previous response (Paper No. 16). The evidence of Exhibits E and F of the previous response (Paper No. 16) indicated the relationship between the amino acid sequence encoded by SEQ ID NO:23 of the present invention and the amino acid sequence of GenBanK accession no. NP_115972, identified as ATP-binding cassette, sub-family C, member 11 isoform a; multi-resistance protein 8. In further support of Applicant's assertions, enclosed as **Exhibit A** is the result of an amino acid sequence comparison between SEQ ID NO:24 of the present invention and accession number NP_660187, annotated by others as ATP-binding cassette, sub-family C, member 11 isoform b; multi-resistance protein 8.
The results of this comparison, clearly, provide further support for the credibility of Applicants' assertion that the sequences of the present invention encode a novel human transporter protein, an ATP-binding cassette, sub-family C, member 11 isoform.

While it is true that there is no part of Yabuuchi *et al.* or Tammur *et al.* that specifically identifies SEQ ID NO:23 of the present as a splice variant of ABCC11. It is also true that, clearly, both scientific groups, Yabuuchi *et al.* and Tammur *et al.* , recognize the utility of ABCC11. Further recognition of the utility of ABCC11 sequences are provided by other scientific publications, such as that of Turriziani, *et al.*, (Impaired 2',3'-dideoxy-3'-thiacytidine accumulation in T-lymphoblastoid cells as a mechanism of acquired resistance independent of multidrug resistant protein 4 with a possible role for ATP-binding cassette C11, Biochem. J. 368, 325-332 ,2002). Turriziani, *et al.*, describe
the finding that increased expression of ATP-binding cassette C11 (ABCC11) was observed in the CEM 3TC cells and that the decreased 3TC accumulation in the CEM 3TC might be due to the upregulation of ABCC11.

As further evidence of the level of acceptance by those of skill in the art of the utility of ATP-binding cassette C11 transporters is provided by the NCBI LocusLink (http://www.ncbi.nlm.nih.gov/LocusLink/LocRpt.cgi?l=85320) summary for ABCC11 genetic locus.

> "The protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes."
>
> "This ABC full transporter is a member of the MRP subfamily which is involved in

multi-drug resistance. It is expressed at low levels in all tissues, except kidney, spleen, and colon. This gene and family member ABCC12 are determined to be derived by duplication and are both localized to chromosome 16q12.1. Their chromosomal localization, potential function, and expression patterns identify them as candidates for paroxysmal kinesigenic choreoathetosis, a disorder characterized by attacks of involuntary movements and postures, chorea, and dystonia. Multiple alternatively spliced transcript variants have been described for this gene."

Clearly the utility of ABCC 11 transporter proteins, and thus logically the sequences of the present invention which encode an ABCC11 transporter protein isoform, have a very well established utility that is readily recognized by those of skill in the art.

In addition to the previously submitted Exhibits, demonstrating that the sequences of the present invention encode an ABCC11 isoform. Genetic mapping of the sequences of the present invention indicate that they are contained in 25 non-contiguous exons which are contained in BAC clone AC007600 (as shown in **Exhibit B**) and maps to human chromosome 16. Furthermore, the GenBanK accession numbers NP_115972 and NP_660187, whose clear homology and large regions of identity with the sequences of the present invention have been evidenced, map to the same genetic locus, 16q12.1. This is the same region that is known to contain the ABCC11 gene.

Applicants have thus demonstrated that the sequences of the present invention share an extremely high level of homology and large regions of identity with at least two proteins, identified by others to encode two isoforms of ATP-binding cassette, sub-family C, member 11; multi-resistance protein 8. Furthermore, the sequences of the present invention, the two highly homologous proteins and the ABCC11 gene map to the same genetic locus on human chromosome 16. This clearly demonstrates that Applicants' assertion that the present invention is a transporter protein, a novel isoform of the ABCC11 transporter protein. The activity, function and utility of ABCC11 transporters is well established and known to those of skill in the art, and thus clearly the utility of novel isoform of ABCC11 would be readily be recognized by those of skill in the art.

The Action also discounts Applicants' assertion regarding the use of the presently claimed polynucleotides on DNA chips, based on the position that such a use would allegedly be generic.

Further, the Action seems to be requiring Applicants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of § 101. Applicants respectfully point out that knowledge of the exact function or role of the presently claimed sequence is not required to track expression patterns using a DNA chip. As set forth in Applicants First Response, given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. The claimed sequence provides a specific marker of the human genome (see evidence below), and that such specific markers are targets for discovering drugs that are associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, as well as more recently issued U.S. Patent Nos. 5,837,832, 6,156,501 and 6,261,776. Accordingly, the present sequence has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful.

Additionally, since only a small percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. Thus, not all human genomic DNA sequences are useful in such gene chip applications, further discounting the Examiner's position that such uses are "generic". Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats,

for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value that it was acquired by large pharmaceutical company, Merck & Co., for substantial sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

In addition, the sequences of the present invention have particularly specific utility in DNA gene chip based analysis as they have been identified to contain several coding region single nucleotide polymorphisms (cSNPs), thus increasing their utility in DNA gene chip based analysis. The first polymorphism identified is a A to G transition at position 704 of, for example, SED ID NO: 23, which results in a corresponding change of gln to an arg at, for example, position 235 of SEQ ID NO:24; the second can occur at position 2184 of, for example, SEQ ID NO:23 that changes a gln to a his at position 728 of, for example, SEQ ID NO:24; and the third cSNP involves a silent T to C transition at position 2,436 of, for example, SEQ ID NO:23.

Further evidence of utility of the presently claimed polynucleotide, although only one is needed to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), is the utility the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification and evidenced below. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the

gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences (see evidence below). In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.,* showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

As still further evidence supporting Applicants assertions of the specific utility of the sequences of the present invention in localizing the specific region of the human chromosome and identification of functionally active intron/exon splice junctions is the information provided in **Exhibit B**. This is the result of a blast analysis using SEQ ID NO:23 of the present invention when compared to the identified human genomic sequence. This result indicates that the sequence of the present invention is encoded by 25 exons spread non-contiguously along a region of human chromosome 16, which is contained within represented by clone, AC0076005. Thus clearly one would not simply be able to identify the 25 protein encoding exons that make up the sequence of the present intention from within the large genomic sequence. Nor, would one be

able to map the protein encoding regions identified specifically by the sequences of the present invention without knowing exactly what those specific sequences were.

Finally, the Examiner has determined that applicants argument of due process presented in previous response is not persuasive. Applicants understanding is that issued United States patents retain a legal presumption of validity which in this case indicates that the inventions claimed in the cited patents are *legally presumed* to be in full compliance with the provisions of 35 U.S.C. sections 101, 102, 103, and 112. Applicants respectfully submit that, absent a change in the law as enacted by Congress and signed by the President, it is improper for the Examiner to hold Applicants' invention to a different legal standard of patentability. Given the rapid pace of development in the biotechnology arts, it is difficult for the Applicants to understand how an invention fully disclosed and free of prior art at the time the present application was filed, could somehow retain *less* utility and be *less* enabled than inventions in the cited issued U.S. patents (which were filed during a time when the level of skill in the art was clearly lower). Simply put, Applicants invention is *more* enabled and retains *at least as much* utility as the inventions described in the claims of the U.S. patents of record. Any argument to the contrary is at best arbitrary and at worst capricious. Absent authority provided by an act of Congress or Executive order, arbitrary or capricious conduct by an administrative office the U.S. government has historically proven to conflict with the provisions of the U.S. Constitution. The Patent Office does not have the authority to rewrite U.S. law. However, the Patent Office does have a Constitutional obligation to administer U.S. law in an unbiased and procedurally consistent manner. That is what the Applicants are respectfully requesting the Examiner to consider in the present matter.

For each of the foregoing reasons, Applicants submit that in light of the above discussion and those presented in previous Applicant responses, the presently claimed invention has been shown to have a substantial, specific, credible and well-established utility and that the rejection of pending claims 1, 5-7 under 35 U.S.C. § 101 has been avoided, and respectfully request that the rejection be withdrawn.

## IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action continues to reject the claims under 35 U.S.C. § 112, first paragraph, since

allegedly one skilled in the art would not know how to use the claimed invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully disagree. As demonstrated extensively in the section above, the present invention is supported by a specific, substantial, credible and well-established utility. The function of the protein encoded by the sequences of the present invention is that of a transporter, more specifically ABC transporter 11. Thus, Applicants submit that as the claims have been shown to have a specific, substantial, credible and well established utility, as detailed in the section above, Applicants respectfully request that the rejection of claims 1, 5-7 under 35 U.S.C. § 112, first paragraph, be withdrawn.

## V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Landsman have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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April 18, 2003

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